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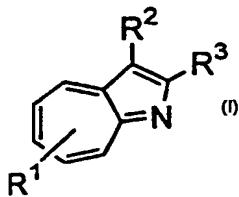
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(54) Title: AZAAZULENE INHIBITORS OF P38 MAP KINASE AND TNF-ALPHA



(57) Abstract: Compounds having the formula (I) are useful for treating diseases caused by unregulated p38 MAP kinase or TNF-alpha activity. Pharmaceutical compositions containing the compounds, methods of treatment using the compounds, and preparation of the compounds are also disclosed.

AZAAZULENE INHIBITORS OF P38 MAP KINASE AND TNF-ALPHATechnical Field

5 The instant invention relates to azaazulene compounds useful for treating diseases caused or exacerbated by unregulated p38 MAP kinase or TNF-alpha activity, pharmaceutical compositions containing the compounds, preparation of the compounds, and methods of treatment using the compounds.

Background of The Invention

10 Cytokine mediated diseases are diseases involving unregulated production of one or more cytokines. Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) are cytokines produced by cells involved in immunoregulation and other physiological conditions such as inflammation.

15 TNF-alpha, upstream in the cytokine cascade of inflammation, is a potent proinflammatory mediator implicated in inflammatory conditions such as arthritis, asthma, septic shock, non-insulin dependent diabetes mellitus, and inflammatory bowel disease. Elevated levels of TNF-alpha have also been shown to produce elevated levels of IL-1. Inhibition of TNF-alpha, therefore, should reduce levels of IL-1 and ameliorate disease states caused by unregulated IL-1 synthesis. Such disease states include rheumatoid 20 arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft versus host reaction, allograft rejections, fever and myalgias due to infection, cachexia secondary to infection or 25 malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, and pyresis.

IL-1 has been shown to mediate a variety of biological activities such as the activation of T-helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, and the suppression of plasma iron levels (*Rev. Infect. Disease*, 6, 51 (1984)). Elevated levels of IL-1 have also been implicated in mediating or exacerbating a number of disease states including rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease, ulcerative colitis, anaphylaxis, muscle degeneration, cachexia, Reiter's syndrome, type I and type II diabetes, bone resorption diseases, ischemia reperfusion injury, atherosclerosis, brain trauma, multiple sclerosis, sepsis, septic shock, and toxic shock syndrome. Viruses sensitive to TNF-alpha inhibition, such as HIV-1, HIV-2, HIV-3, are also affected by IL-1 production. In rheumatoid arthritis, both IL-1 and TNF-alpha induce collagenase synthesis and ultimately lead to tissue destruction within arthritic joints (*Lymphokine Cytokine Res.* (11):253- 256, (1992) and *Clin. Exp. Immunol.* 898:244-250, (1992)).

P38 MAP (mitogen-activated protein) kinase has been shown to play a role in the inflammatory stress induced biochemical pathway for the production of IL-1 and TNF-alpha (*Nature*, 1994, 372, 739-745). Inhibiting p38 MAP kinase reduces levels of TNF-alpha and can therefore be useful for treating disease states involving the same (*FEBS Lett.* 1995, 364, 229-233). Such diseases include rheumatoid arthritis, osteoarthritis, endotoxemia, toxic shock syndrome, and other acute or chronic inflammatory diseases such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease, tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis, acute synovitis, and angiofollicular lymphoid hyperplasia.

Because of the clinical potential for compounds which inhibit unregulated TNF-alpha production or p38 MAP kinase activity, these compounds and their structural analogs are the subject of current research.

US 5,502,187 reports that diamino substituted azaindole compounds are useful in the treatment of inflammatory diseases.

WO 94/14434 and WO 95/33748 report classes of substituted indole endothelin receptor antagonists useful for treating hypertension, renal failure and cerebrovascular disease.

5 DE 2909779-A1 reports a related class of substituted indoles useful for treatment of atherosclerosis.

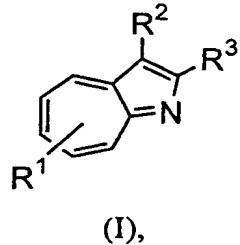
US 3,551,567, FR 1587692, DE 1795061, *Ukr. Kim. Zh.* (Russ. Ed.) (1982), 48(I), 76-9; *Khim. Geterotsikl. Soedin.* (1980), (7), 959-64 also report the preparation of 3-(4-pyridyl)indoles.

10 US 3,654,308, US 3,565,912, and FR 10 1505197 report the preparation of 2,3-diphenylindole derivatives.

However, there remains a need for compounds which inhibit TNF-alpha production and p38 MAP kinase activity with modified or improved profiles of activity.

Summary of The Invention

15 In its principle embodiment, the present invention discloses p38 MAP kinase and TNF-alpha inhibiting compounds represented by structural formula (I):



20 or a pharmaceutically acceptable salt or prodrug thereof, wherein

R^1 is selected from the group consisting of hydrogen, amino, hydroxy, hydroxyalkyl, and $CH_3S(O)_t$ -, wherein t is zero, one, or two;

25 R^2 and R^3 are independently selected from the group consisting of phenyl, naphthyl, furyl, thiophenyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidyl, and pyrazinyl, wherein the groups defining R^2 can be optionally substituted with one, two, or three substituents independently selected from the group consisting of C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_6 perfluoroalkyl, hydroxy,

C₁-C₃ alkoxy, trifluoromethoxy, trifluorothiomethoxy, cyano, nitro, carboxyl, and amino, and wherein the groups defining R³ can be optionally substituted with one, two, or three substituents independently selected from the group consisting of carboxyl, cyano, halide, nitro, hydroxyl, oxo, C₁-C₆ perfluoroalkoxy, sulfonic, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluorothioalkoxy, sulfhydryl, thiolcarboxyl, thioxo, -L¹-L²-R⁴, and -L¹-L³-R⁵;

5 L¹ is absent or -L⁴-(C₁-C₆ alkylene)-;

L² is selected from the group consisting of -C(=O)(NR⁶)-, -C(=O)-S-, -N(R⁶)-, =N-, -O-C(=O)-N(R⁶)-, =N-N(R⁶)-, -N(R⁶)-N(R⁶)-, N(R⁶)-C(=NR⁶)-N(R⁶)-, =N-O-, =N-N(R⁶)-C(=O)-N(R⁶)-, and -N(R⁶)-C(=O)-N(R⁶)-;

10 L³ is absent or selected from the group consisting of -L²-, -C(=O)-, -O-C(=O)-, -N(R⁶)-C(=O)-, -N(R⁶)-C(=O)-O-, -O-, -S-C(=O)-, -O-C(=O)-O-, =N(R⁶)-O-, -O-C(=N(R⁶))-, -N(R⁶)-C(=NR⁶)-, -C(=O)-O-C(=O)- and -S(O)_n-, wherein n is zero, one, or two;

L⁴ is absent or is selected from the group consisting of -O-, -S(O)_n-, and

15 -N(R⁶)-;

R⁴ is hydrogen or C₁-C₆ alkyl;

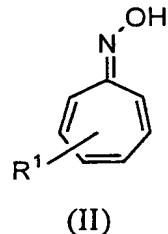
R⁵ is selected from the group consisting of C₁-C₆ alkyl, C₃-C₆ cycloalkyl, cycloalkylalkyl, and arylalkyl;

and

20 R⁶ is selected from the group consisting of hydrogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, cycloalkylalkyl, and arylalkyl.

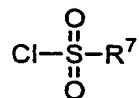
In another embodiment, the instant invention discloses a method for preparing the compound of formula (I) comprising

(a) reacting a compound of formula (II)



with a compound of formula (III)

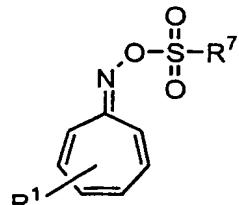
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(III),

wherein R^7 is selected from the group comprising methyl, trifluoromethyl, and phenyl, wherein the phenyl group can be optionally substituted with a substituent selected from the group comprising methyl, bromo, and nitro,

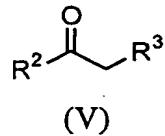
5 and a first base to provide a compound of formula (IV)



(IV)

and

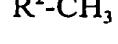
10 (b) reacting the product of step (a) with a compound of formula (V)



(V)

and a second base.

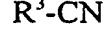
In yet another embodiment, the instant invention discloses a method for preparing
 15 the compound of formula (I) comprising
 (a) reacting a compound of formula (VI)



(VI)

with a third base;

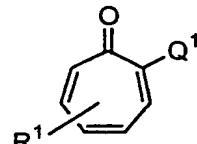
20 (b) reacting the product of step (a) with a compound of formula (VII)



(VII);

and

(c) reacting the product of step (b) with a compound of formula (VIII)



(VIIID)

wherein Q¹ is selected from the group comprising chlorine, bromine and iodine.

In still yet another embodiment, the instant invention discloses a method of
5 inhibiting p38 MAP kinase in a mammal, comprising administering to the mammal a
therapeutically effective amount of a compound of formula (I).

In still yet another embodiment, a method of inhibiting TNF-alpha production in a mammal, in recognized need of such treatment, comprising administering to the mammal a therapeutically effective amount of a compound of Claim 1.

10 In still yet another embodiment, the instant invention discloses a method of treating inflammatory diseases in a mammal, in recognized need of such treatment, comprising administering to the mammal a therapeutically effective amount of a compound of formula (I).

In still yet another embodiment, the instant invention discloses a method of
15 treating inflammatory diseases in a mammal comprising administering to the mammal, in
recognized need of such treatment, a therapeutically effective amount of a compound of
formula (I) in the presence of a pharmaceutically acceptable carrier.

Detailed Description of the Invention

20 The instant invention discloses compounds which inhibit the p38 MAP kinase activity and TNF-alpha production and are therefore useful as anti-inflammatory compounds. The compounds of the instant invention comprise an azaazulene ring formed by fusion of a pyrrole ring to a cycloheptatriene ring. The azaazulene ring is optionally substituted on the cycloheptatriene ring by replacement of a hydrogen atom thereon by the 25 radicals defining R¹ and on the two available positions of the pyrrole ring by independent replacement of the hydrogen atoms thereon by radicals defining R² and R³.

Definition of Terms

As used in the specification, the following terms have the meanings indicated:

The term "alkoxy," as used herein, refers to an alkyl group connected to the parent molecular group through an oxygen atom. The alkoxy groups of this invention can be optionally substituted.

The term "alkyl," as used herein, refers to a monovalent straight or branched chain saturated hydrocarbon having from one to six carbon atoms. The alkyl groups of this invention can be optionally substituted.

The term "alkylene," as used herein, refers to a divalent straight or branched chain saturated hydrocarbon having from one to six carbon atoms. The alkylene groups of this invention can be optionally substituted.

The terms "amino," and "amino group," as used herein, refer to -NH₂ or a derivative thereof formed by independent replacement of one or both hydrogen atoms thereon with C₁-C₆ alkyl, C₃-C₈ cycloalkyl, aryl, arylalkyl, and heteroaryl.

The term "aryl," as used herein, refers to a monocyclic-ring system, or a bicyclic- or a tricyclic- fused ring system wherein one or more of the fused rings are aromatic. Representative examples of aryl include, but are not limited to, anthracenyl, azulenyl, fluorenyl, indanyl, indenyl, naphthyl, phenyl, and tetrahydronaphthyl.

The term "arylalkyl," as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, and 2-naphth-2-ylethyl.

The term "azido," as used herein, refers to -N₃.

The term "carboxaldehyde," as used herein, refers to -CHO.

The term "carboxyl," as used herein, refers to -CO₂H. The carboxyl groups of this invention can be optionally protected with carboxyl protecting groups.

The term "carboxyl protecting group," as used herein, refers to selectively removable groups which protect hydroxyl groups against undesirable side reactions during synthetic procedures and includes all conventional carboxyl protecting groups. Examples

of carboxyl groups include optionally substituted alkyl groups such as methyl, ethyl, n-propyl, isopropyl, 1,1-dimethylpropyl, n-butyl, and tert-butyl; aryl groups such as phenyl, and naphthyl; optionally substituted arylalkyl groups such as benzyl, diphenylmethyl, triphenylmethyl, para-nitrobenzyl, para-methoxybenzyl, and bis(para-methoxyphenyl)methyl; optionally substituted acylalkyl groups such as acetyl methyl, benzoyl methyl, para-nitrobenzoyl methyl, para-bromobenzoyl methyl, and para-methanesulfonylbenzoyl methyl; optionally substituted oxygen-containing heterocyclic groups such as 2-tetrahydropyranyl and 2-tetrahydrofuryl; optionally substituted haloalkyl groups such as 2,2,2-trichloroethyl; optionally substituted alkylsilylalkyl groups such as 2-(trimethylsilyl)ethyl; optionally substituted acyloxyalkyl groups such as acetoxy methyl, propionyloxymethyl, and pivaloyloxymethyl; optionally substituted nitrogen-containing heterocyclic groups such as phthalimidomethyl and succinimidomethyl; optionally substituted cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl; optionally substituted alkoxyalkyl groups such as methoxymethyl, methoxyethoxymethyl, and 2-(trimethylsilyl)ethoxymethyl; optionally substituted arylalkoxyalkyl groups such as benzyloxymethyl; optionally substituted alkylthioalkyl groups such as methylthiomethyl and 2-methylthioethyl; optionally substituted arylthioalkyl groups such as phenylthiomethyl; optionally substituted alkenyl groups such as 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, and allyl; and optionally substituted silyl groups such as trimethylsilyl, triethylsilyl, triisopropylsilyl, diethylisopropylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, diphenylmethylsilyl, and tert-butylmethoxyphenylsilyl.

The term "cyano," as used herein, refers to -CN.

The term "cycloalkyl," as used herein, refers to a monovalent saturated cyclic or bicyclic hydrocarbon having three to ten carbon atoms. The cycloalkyl groups of this invention can be optionally substituted.

The term "cycloalkylalkyl," as used herein, refers to cycloalkyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

The terms "halo" or "halide" as used herein, refer to F, Cl, Br, or I.

The term heteroaryl as used herein refers to an aromatic heterocycle selected from the group consisting of furyl, thiophenyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidyl, and pyrazinyl.

5 The term "hydroxy," as used herein, refers to an -OH group.

The term "hydroxyalkyl," as used herein, refers to a hydroxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

The term "nitro," as used herein, refers to -NO₂.

The term "oxo," as used herein, refers to a group formed by the replacement of two hydrogen atoms on the same carbon atom with a single oxygen atom.

10 The term "perfluoroalkoxy," as used herein, refers to a perfluoroalkyl group attached to the parent molecular group through an oxygen atom.

The term "perfluoroalkyl" as used herein, refers to a monovalent straight or branched chain saturated hydrocarbon having from one to six carbon atoms, wherein all of the hydrogens have been replaced with fluorines.

15 The term "perfluorothioalkoxy," as used herein, refers to a perfluoroalkyl group attached to the parent molecular group through a sulfur atom.

The term "pharmaceutically acceptable prodrugs," as used herein, refers to prodrugs of the compounds which are suitable for treatment of inflammatory diseases without undue toxicity, irritation, and allergic response, which are commensurate with a 20 reasonable benefit/risk ratio, and which are effective for their intended use.

The term "prodrug," as used herein, represents compounds which are rapidly transformed *in vivo* to the parent compounds, such as, for example, by hydrolysis in blood. Prodrugs of the invention can include compounds wherein a nitrogen on the molecule has attached thereto an aminoacyl (1-mer), diaminoacyl (2-mer), or triaminoacyl (3-mer)

25 group optionally capped with a carboxyl protecting group. The term "aminoacyl," as used herein, refers to a group derived from naturally or unnaturally occurring amino acid in the racemic, D or L configuration. The terms "bisaminoacyl" and "triaminoacyl," as used herein, refer to di- and tri- aminoacyl groups, respectively. Other prodrugs of the invention include compounds wherein a carboxylic acid or amine group of the compounds 30 is attached thereto a 2-oxo-1,3-dioxol-4-yl)methyl group. Still other prodrugs of the

invention include compounds wherein a tertiary amine group on the compounds has attached thereto a N-phosphonooxymethyl group.

The term "pharmaceutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds which are water or oil-soluble or dispersible and are 5 suitable for treatment of inflammatory diseases without undue toxicity, irritation, and allergic response, which are commensurate with a reasonable benefit/risk ratio, and which are effective for their intended use. The salts may be prepared during the final isolation and purification of the compounds or separately by reacting a free base group with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, 10 aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 15 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, trichloroacetic, trifluoroacetic, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with alkyl halides such as 20 methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates such as dimethyl, diethyl, dibutyl, and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides; arylalkyl halides such as benzyl and phenethyl bromides. Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric and organic acids such as oxalic, maleic, succinic, and citric.

Basic addition salts can be prepared during the final isolation and purification of 25 the compounds by reacting a carboxylic acid-containing group such as the one at the C-3 position of the quinoline or naphthyridine with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, 30 magnesium, and aluminum salts and nontoxic quaternary ammonia and amine cations such

as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N-dibenzyl-phenethylamine, 1-ephenamine, 5 and N,N'-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

The term "sulphydryl," as used herein, refers to -SH.

The term "sulfonic," as used herein, refers to -SO₃H.

10 The term "thiolcarboxyl," as used herein, refers to -C(=O)SH.

The term "thioxo," as used herein, refers to a group formed by the replacement of two hydrogen atoms on the same carbon atom with a single sulfur atom.

In accordance with pharmaceutical compositions and methods of treatment of the invention, the compounds can be administered alone or in combination with other anti-inflammatory agents. When using the compounds, the specific therapeutically effective dose level for any particular patient will depend upon factors such as the disorder being treated and the severity of the disorder; the activity of the particular compound used; the specific composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration; the route of administration; the rate of excretion of the 15 compound employed; the duration of treatment; and drugs used in combination with or coincidentally with the compound used. The compounds can be administered orally, parenterally, osmotically (nasal sprays), rectally, vaginally, or topically in unit dosage formulations containing carriers, adjuvants, diluents, vehicles, or combinations thereof. The term "parenteral" includes infusion as well as subcutaneous, intravenous, 20 intramuscular, and intrasternal injection.

Parenterally administered aqueous or oleaginous suspensions of the compounds can be formulated with dispersing, wetting, or suspending agents. The injectable preparation can also be an injectable solution or suspension in a diluent or solvent. Among the acceptable diluents or solvents employed are water, saline, Ringer's solution, 25 buffers, monoglycerides, diglycerides, fatty acids such as oleic acid, and fixed oils such as

monoglycerides or diglycerides.

The anti-inflammatory effect of parenterally administered compounds can be prolonged by slowing their absorption. One way to slow the absorption of a particular compound is administering injectable depot forms comprising suspensions of crystalline, 5 amorphous, or otherwise water-insoluble forms of the compound. The rate of absorption of the compound is dependent on its rate of dissolution which is, in turn, dependent on its physical state. Another way to slow absorption of a particular compound is administering injectable depot forms comprising the compound as an oleaginous solution or suspension. Yet another way to slow absorption of a particular compound is administering injectable 10 depot forms comprising microcapsule matrices of the compound trapped within liposomes, microemulsions, or biodegradable polymers such as polylactide-polyglycolide, polyorthoesters or polyanhydrides. Depending on the ratio of drug to polymer and the composition of the polymer, the rate of drug release can be controlled.

Transdermal patches can also provide controlled delivery of the compounds. The 15 rate of absorption can be slowed by using rate controlling membranes or by trapping the compound within a polymer matrix or gel. Conversely, absorption enhancers can be used to increase absorption.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In these solid dosage forms, the active compound can optionally comprise 20 diluents such as sucrose, lactose, starch, talc, silicic acid, aluminum hydroxide, calcium silicates, polyamide powder, tableting lubricants, and tableting aids such as magnesium stearate or microcrystalline cellulose. Capsules, tablets and pills can also comprise buffering agents, and tablets and pills can be prepared with enteric coatings or other release-controlling coatings. Powders and sprays can also contain excipients such as talc, 25 silicic acid, aluminum hydroxide, calcium silicate, polyamide powder, or mixtures thereof. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons or substitutes therefor.

Liquid dosage forms for oral administration include emulsions, microemulsions, 30 solutions, suspensions, syrups, and elixirs comprising inert diluents such as water. These compositions can also comprise adjuvants such as wetting, emulsifying, suspending,

sweetening, flavoring, and perfuming agents.

Topical dosage forms include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, and transdermal patches. The compound is mixed under sterile conditions with a carrier and any needed preservatives or buffers. These dosage forms can also include excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof. Suppositories for rectal or vaginal administration can be prepared by mixing the compounds with a suitable nonirritating excipient such as cocoa butter or polyethylene glycol, each of which is solid at ordinary temperature but fluid in the rectum or vagina. Ophthalmic formulations comprising eye drops, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

The total daily dose of the compounds administered to a host in single or divided doses can be in amounts from about 0.1 to about 200 mg/kg body weight or preferably from about 0.25 to about 100 mg/kg body weight. Single dose compositions can contain these amounts or submultiples thereof to make up the daily dose.

Preferred embodiments of the instant invention include compounds of formula (I), wherein R¹ is hydrogen; compounds of formula (I), wherein R² is optionally substituted pyridyl; compounds of formula (I), wherein R² is optionally substituted pyrimidinyl; and compounds of formula (I), wherein R³ is optionally substituted phenyl.

Specific compounds of the instant invention include 2-(4-fluorophenyl)-3-(4-pyridinyl)cyclohepta[b]pyrrole, 2-(4-fluorophenyl)-3-(2-fluoropyridin-4-yl)cyclohepta[b]pyrrole, 3-pyridin-4-yl-2-(3-(trifluoromethyl)phenyl)cyclohepta[b]pyrrole, 2-(4-fluorophenyl)-3-(2-(methylsulfanyl)-4-pyrimidinyl)cyclohepta[b]pyrrole, 4-(2-(4-fluorophenyl)cyclohepta[b]pyrrol-3-yl)-N-methyl-2-pyrimidinamine, N-methyl-4-{2-(3-(trifluoromethyl)phenyl)cyclohepta[b]pyrrol-3-yl}pyrimidin-2-amine, 3-(2-fluoropyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)cyclohepta[b]pyrrole, 2-(4-methoxyphenyl)-3-pyridin-4-ylcyclohepta[b]pyrrole,

2-(4-chlorophenyl)-3-pyridin-4-ylcyclohepta[b]pyrrole,
2-(3-chlorophenyl)-3-pyridin-4-ylcyclohepta[b]pyrrole,
2-(3-chlorophenyl)-3-(2-fluoropyridin-4-yl)cyclohepta[b]pyrrole,
and
5 2-(4-methylphenyl)-3-pyridin-4-ylcyclohepta[b]pyrrole.

Determination of Biological Activity

p38 MAP kinase Inhibitory Activity

10 The p38 MAP kinase enzyme was cloned according to the procedure described in
Journal of Biomolecular Screening, 1999, 4(3), 129-135.

15 *In Vitro* p38 MAP Kinase Assay. The inhibitory activity and potency of
compounds of the invention were evaluated in a p38 MAP kinase assay. The inactive,
baculovirus expressed human p38 MAP kinase was activated by partially purified rabbit
MKK6/SKK3/MEK6 enzyme (Upstate Biotechnology). The p38 MAP kinase and MKK6
enzymes were diluted in assay buffer-I: (25 mM HEPES (pH 7.4), 25 mM glycerol
20 mM phosphate, 2 mM MgCl₂, 50 mM EDTA, 1 mM NaF, 1 mM Na₃VO₄, 1 mM DTT and 50
mM ATP) to 0.035 µg/L and 0.2 U/L, respectively and incubated for 90 minutes at 30 °C.
20 µL of activated p38 MAP kinase and 10 µL of 10X test compounds were pre-incubated
in 96-well flexible assay plates (Becton Dickinson) for a minimum of 15 minutes in assay
buffer-II (same as I containing 10 µM ATP). Next, 10 µL of E. coli expressed,
thioredoxin fused-ATF2 [(aa 1-109) Abbott Laboratories, Abbott Park, IL)] substrate
peptide (0.75 µg/µL) was added to all wells except those representing background values.
The p38 MAP kinase reaction was started by the addition of 30 µL of [γ -33P] ATP diluted
to 0.033 µCi/µL in assay buffer II and was allowed to proceed for 60 minutes at 30 °C.
25 The p38 MAP kinase activity was halted by the addition of 50 µL/well of stop buffer
containing 5% H₃PO₄. Approximately 60% of the stopped reaction volumes were then
transferred to corresponding phosphocellulose filter-wells of a 96-well Multiscreen®
filtration plate (Millipore) prewetted with 1% H₃PO₄ and incubated for 15 minutes at
ambient temperature. The reaction volumes were vacuum-filtered and washed 3 times
30 each with 1% H₃PO₄ using a Multiscreen® vacuum manifold (Millipore). The filter-wells

were dried for approximately 5 minutes on the vacuum manifold. After drying, 50 μ L of Microscint-20 (Packard) was added to each filter-well and the plates were counted in a Topcount microtiter plate scintillation counter (Packard). Potency determinations were made using standard logit-regression analysis of individual compound dose responses.

5 The results are shown in Table 1.

TNF-alpha Inhibitory Activity

In Vitro TNF-alpha Assay. Cell-based, *in vitro* assay for measuring inhibition of lipopolysaccharide (LPS)-induced TNF-alpha secretion by an acute monocytic leukemia 10 cell line (THP-1). Compounds were tested for inhibition of TNF-alpha secretion from LPS-stimulated THP-1 cells. THP-1 cells (ATCC) were maintained as a suspension culture in exponential phase of growth in complete growth medium containing RPMI-1640 (Sigma) supplemented with 1 mM MEM-sodium pyruvate (Gibco BRL), 1X MEM- 15 nonessential amino acids (Sigma), 10% defined fetal bovine serum (Hyclone), 30 μ M 2-mercaptoethanol (Sigma), and an antibiotic/L-glutamine solution consisting of 25 units/mL penicillin; 25 μ g/mL streptomycin and 2 mM L-glutamine (Gibco BRL). For the assay, the THP-1 cells were removed from culture and washed once in Dulbecco's phosphate buffered saline (Gibco BRL) by centrifugation at 400 xg for 10 min. After washing, the cells were resuspended in fresh growth medium at approximately 1.5-2 $\times 10^6$ 20 cells/ml. Test compounds were solubilized in 100% DMSO and diluted to the appropriate 4X concentration. Lipopolysaccharide (LPS) from *Salmonella typhimurium* was diluted to 8 μ g/mL in growth medium. To all wells of a flat-bottom, 96-well, Costar tissue culture plate (Corning Incorporated), 50 μ L of test compound and 100 μ L of the THP-1 cell 25 suspension were added and incubated for a minimum of 15 minutes at ambient temperature. Activation of the THP-1 cells and the subsequent secretion of TNF-alpha was initiated by the addition of 50 μ L of LPS to all wells except those representing background values. After 4 hours in a 37 °C humidified incubator with 5% CO₂, all plates were centrifuged at 400 xg for 10 minutes to clear the conditioned medium of THP-1 cells. 30 150 μ L of TNF-alpha conditioned medium from each well of the culture plates was transferred to the corresponding wells of sterile, round-bottom, 96-well, Costar tissue

culture plates (Corning Incorporated, Acton MA) and stored at -20 °C. TNF-alpha was quantitated using an ELISA with a dynamic range of 31.25 pg/mL to 2 ng/mL. Potency determinations were made using standard logit-regression analysis of individual compound dose responses. The results are shown in Table 2.

5

Table 1.

Example	IC ₅₀ (nm)
1	1340
2	3280
3	1470
4	2590
5	17100
6	2850
7	12090
8	24060
9	2790
10	4960
11	935
12	4760

Table 2.

Example	IC ₅₀ (nm)
1	230
2	1557
3	160
4	4510
5	1713
6	675
7	1606
8	37%@10µm
9	1399
10	1419
11	950
12	263

Thus, the compounds of the invention inhibit p38 MAP kinase and TNF-alpha and are therefore useful for treating diseases caused or exacerbated by unregulated p38 MAP kinase and TNF-alpha activity.

Synthetic Methods

The compounds and processes of the invention will be better understood in connection with the following schemes which illustrate methods by which the compounds of the invention can be prepared. The compounds of the invention can be prepared by a

15

variety of procedures. Representative procedures are shown in Schemes 1-5, wherein R¹ through R⁶ are defined above and R⁷ is methyl, trifluoromethyl, and phenyl, wherein the phenyl group can be optionally substituted with a substituent selected from the group comprising methyl, bromo, and nitro.

5 It will be readily apparent that other compounds of the invention can be synthesized by the substitution of appropriate starting materials and reagents in the syntheses shown below. It will also be apparent that protection and deprotection steps, as well as the order of the steps themselves, can be carried out in varying order to successfully complete the syntheses of compounds of the instant invention. Commonly 10 used protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1999)).

Starting materials and reagents are available commercially or can be prepared synthetically by known methods such as those disclosed in Larock, "Comprehensive 15 Organic Transformation. A Guide to Functional Group Preparations," VCH Publishers, New York (1989).

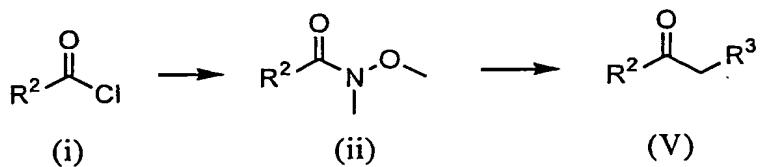
All of the reactions discussed in the schemes are run in solvents or mixtures of solvents in which the starting materials and products are not reactive, unless otherwise specified, and those in which the starting materials are at least partially soluble. The appropriate solvent for each reaction will be apparent to one skilled in the art. Preferred 20 solvents, used alone or in combination, include THF, dioxane, dichloromethane, chloroform; carbon tetrachloride, 1,2-dichloroethane, acetonitrile, DMF; ethyl acetate, isopropyl acetate, hexanes, heptane, benzene, toluene, anisole, xylene, C₁-C₅ alcohols, water, pyridine; aniline, TEA, N-methylpyrrolidinone, HMPA, diglyme, DME, acetone, cyclohexane, glycerol, tert-butylmethyl ether, diethyl ether, methyl ether, dioxane, N- 25 methylmorpholine, 1,1,1-trichloroethane, trifluoroacetic acid, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid; perchloric acid, and nitric acid.

Abbreviations

Abbreviations used in the descriptions of the schemes and the examples which 30 follow are: DCM for dichloromethane; DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene;

DMF for N,N-dimethyl formamide; DMSO for dimethyl sulfoxide; LDA for lithium diisopropylamide; TBME for tert-butylmethyl ether; THF for tetrahydrofuran; TMSCl for trimethylsilyl chloride; TMSBr for trimethylsilyl bromide; TEA for triethylamine; DME for dimethoxyethane; HMPA for hexamethylphosphoramide; DMAP for N,N-dimethylaminopyridine, NCS for N-chlorosuccinimide; TsCl for para-toluenesulfonic acid chloride; and NBS for N-bromosuccinimide.

Scheme 1



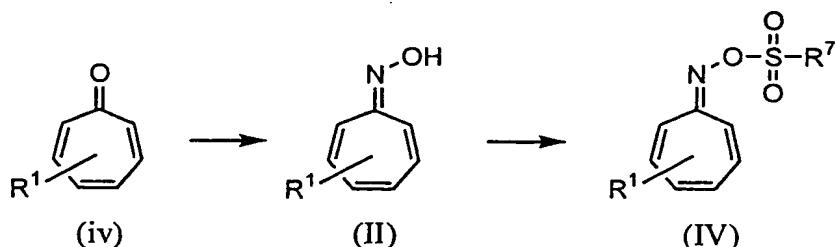
As shown in Scheme 1, the conversion of (i) to (ii) can be accomplished by treating the former with methoxymethylamine hydrochloride and a base in a solvent such as dichloromethane, chloroform, THF, TBME, 1,1,1-trichloroethane, pyridine, or a mixture thereof. Preferred bases include TEA, pyridine, imidazole, diisopropylethylamine, lutidine, and DMAP. Although the reaction generally proceeds at about 0 °C, it can be run at elevated temperatures, as needed. The reaction time is generally about 30 minutes to about 12 hours and can be selected depending on the reaction temperature and the concentration of reactants in the solvent. In a preferred embodiment, a solution of (i) in dichloromethane at about 0 °C is treated with TEA and methoxymethylamine hydrochloride and stirred for about two hours.

The conversion of (ii) to (V) can be accomplished by treating the former with a nucleophile in a solvent such as THF, diethyl ether, TBME, or a mixture thereof. Preferred nucleophiles include Grignard reagents, carbanions, and thioacetate. More preferred are the following nucleophiles: the anion of 4-methylpyridine, the anion of 2-fluoro-4-methylpyridine, and the anion of 4-methyl-2-(methylsulfonyl)pyrimidine.

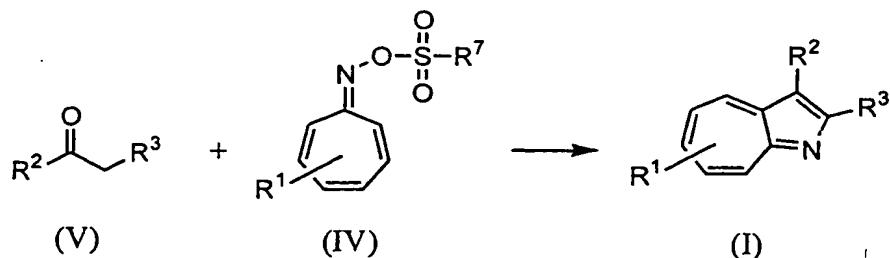
25 Although the reaction generally proceeds at about -78 °C, it can be run at elevated temperatures, as needed. The reaction time is generally about 15 minutes to about 12

hours and can be selected depending on the reaction temperature and the concentration of reactants in the solvent. In a preferred embodiment, a solution of a nucleophile in THF at about -78 °C is treated with a solution of (ii) in THF and stirred for about 3.5 hours.

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Scheme 2

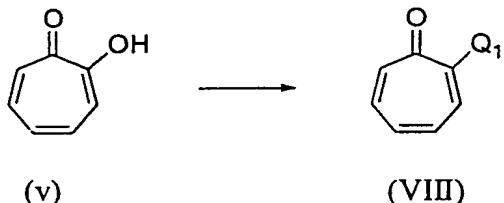
The preparation of (IV) is shown in Scheme 2. The synthesis of (iv), in which R¹ is hydrogen, chloro, bromo, or hydroxy is described in *J. Chem. Soc., Chem. Commun.* 1982, 847. R¹ can be converted into a thioether, a sulfoxide, or a sulfone as described in *J. Organomet. Chem.* 1981, 206(3), C29; a primary amine as described in *J. Chem. Soc., Chem. Commun.* 1983, 1322; substituted amines as described in *J. Organometallic Chem.* 1999, 576, 125-146; or an alcohol as described in *Chem. Lett.* 1985, 997. Methods by which the alcohol can be further oxidized, reduced, or alkylated and the amine can be further oxidized, alkylated, sulfonylated or acylated are well-known in the art. The conversion of (iv) to (II) to (IV) is described in *J. Am. Chem. Soc.* 1995, 117, 1258.

Scheme 3

As shown in Scheme 3, (I) can be prepared by combining (V), (IV), a base, an ammonia source, and a drying agent in a solvent such as benzene, toluene, xylenes, mesitylene, or a mixture thereof. Preferred bases include TEA, diisopropylethylamine, DBU, pyridine, DMAP, and lutidine. Preferred ammonia sources include ammonium

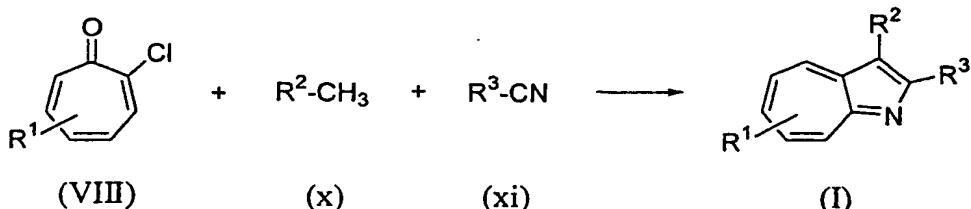
acetate, ammonium chloride, and ammonium sulfate. Preferred drying agents are 3Å or 4Å molecular sieves. Although the reaction generally proceeds at about 70 °C, it can be run at elevated temperatures, as needed. The reaction time is generally about one hour to about 12 hours and can be selected depending on the reaction temperature and the concentration of reactants in the solvent. In a preferred embodiment, a solution of (V), (IV), ammonium acetate, TEA, and 4Å molecular sieves in benzene is heated to about 65-80 °C for about 6 hours.

Scheme 4



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As shown in Scheme 4, the conversion of (v) to (VIII) can be accomplished by treating the former with a halogen source and an optionally added additive in a solvent such as benzene, toluene, xylene, mesitylene, or a mixture thereof. Preferred halogen sources include molecular fluorine, chlorine, bromine, and iodine; mineral acids such as HF, HCl, HBr, and HI; sulfur reagents such as SOCl_2 , TsCl , and SOBr_2 ; silicon reagents such as TMSCl and TMSBr ; phosphorus reagents such as PCl_5 , POCl_3 , P_2I_4 , PCl_3 , PBr_5 ; and miscellaneous chlorinating reagents such as CCl_4 , NCS, and NBS. Preferred additives include triphenylphosphine, DMF, triphenylphosphite, DMAP, and dimethylsulfide. Although the reaction generally proceeds at reflux, it can be run at a lower temperature, as needed. The reaction time is generally about one hour to about 12 hours and can be selected depending on the reaction temperature and the concentration of reactants in the solvent. In a preferred embodiment, a solution of (v) and SOCl_2 in benzene is refluxed for about 1.5 hours.

Scheme 5

As shown in Scheme 5, the synthesis of (I) can be accomplished by treating (xi) with the anion of (x) followed by addition of (VIII), in which the anion of (x) is generated by treating (x) with a base in a solvent such as THF, diethyl ether, TBME, toluene, heptane, ethylbenzene or mixtures thereof. Preferred bases include lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, LDA, and tertiary-butyllithium. Although the reaction generally proceeds at about 0 °C, it may be run at elevated temperature, as needed. The reaction time is generally about one hour to about 24 hours and can be selected depending on the reaction temperature and the concentration of reactants in the solvent. In a preferred embodiment, the anion of (x) is generated by treating a solution of (x) in THF at about 0 °C with a solution of sodium bis(trimethylsilyl)amide in toluene and stirred for about 30 minutes, then (xi) is added. After warming to room temperature, the solution of the anion is treated with (VIII) and stirred for about 16 hours.

The instant invention will now be described in connection with certain preferred embodiments which are not intended to limit its scope. On the contrary, the instant invention covers all alternatives, modifications, and equivalents as can be included within the scope of the claims. Thus, the following examples, which include preferred embodiments, will illustrate the preferred practice of the instant invention, it being understood that the examples are for the purposes of illustration of certain preferred embodiments and are presented to provide what is believed to be the most useful and readily understood description of its procedures and conceptual aspects.

The compounds and processes of the present invention will be better understood in connection with the following examples, which are intended as an illustration of and not a limitation upon the scope of the invention.

Example 12-(4-fluorophenyl)-3-(4-pyridinyl)cyclohepta[b]pyrrole

5

Example 1A4-fluoro-N-methoxy-N-methylbenzamide

Example 1A was made using the method described in *Bioorganic and Medicinal Chemistry Letters* 1997, 5(1), 49. Briefly, para-fluorobenzoyl chloride (31 mL, 260 mmol) was added dropwise to a 0 °C solution of N,O-dimethylhydroxylamine hydrochloride (28 g, 290 mmol) and triethylamine (87 mL, 624 mmol) in DCM (300 mL). The cooling bath was removed, and the reaction mixture stirred for an additional 2 hours. The reaction mixture was then poured into water (200 mL), and extracted with DCM (3x150 mL). The DCM layers were combined, and concentrated. The concentrate was slurried in ethyl acetate and filtered. The filtrate was dried (MgSO_4), filtered, and concentrated to afford 45 g of the desired product as a waxy yellow solid.

Example 1B1-(4-fluorophenyl)-2-(4-pyridinyl)ethanone

n-Butyllithium in hexanes (2.5M, 27.3 mL, 68.25 mmol) was added to a -78 °C solution of diisopropylamine (10.5 mL, 75.90 mmol) in THF (100 mL). After stirring for 20 minutes, 4-methylpyridine (5.3 mL, 54.5 mmol) was added to the reaction mixture. After stirring for 15 minutes, a solution of Example 1A (54.6 mmol) in THF (20 mL) was added dropwise to the reaction mixture. The reaction mixture was warmed to room temperature over 3.5 hours, poured into brine (50 mL), and extracted with 4:1 THF/DCM (3x 50 mL). The combined organic layers were dried (MgSO_4), filtered, and concentrated. The concentrate was purified by column chromatography on silica gel using ethyl acetate as the eluant to afford 4 g of the desired product as a yellow solid.

^1H NMR (300 MHz, CDCl_3): δ 4.27 (s, 2H), 7.19 (m, 4H), 8.3 (m, 2H), 8.57 (m, 2H).

MS (ESI): m/e 216 ($\text{M}+1$)⁺.

Example 1CO-(4-methylphenyl)sulfonyl 2,4,6-cycloheptatrien-1-one oxime

Example 1C was prepared using the method described in *J. Am. Chem. Soc.* 1995, 117, 1258. Briefly, tropone (5 g, 47.1 mmol) in chloroform (15 mL) was added to a 0 °C solution of P_4S_{10} (23 g, 51.7 mmol) and TEA (16.4 mL, 118 mmol) in chloroform (250 mL). After 20 minutes, the reaction mixture was poured into aqueous 5% Na_2CO_3 solution. The layers were separated, and the chloroform was dried ($MgSO_4$), and filtered into a flask containing EtOH (80 mL) and $NH_2OH \cdot HCl$ (9.8 g, 141 mmol). The ethanol/chloroform mixture was cooled to 0 °C and treated with TEA (16.4 mL, 118 mmol). The reaction mixture was allowed to warm to room temperature over a period of two hours. The reaction mixture was poured into 1:1 saturated NH_4Cl :water. The layers were separated and the aqueous layer was back extracted with chloroform (2x50 mL). The combined chloroform layers were concentrated to afford a red slurry which was purified by silica gel column chromatography to afford 4.1 g, (72%) of the desired product.

Para-toluenesulfonyl chloride (2.0 g, 10.5 mmol) was added to a 0 °C solution of tropone oxime (1.2 g, 9.9 mmol) and triethylamine (1.52 mL) in DCM (50 mL). The reaction mixture was slowly warmed to room temperature over 1.5 hours, and then washed with water, and brine, dried (Na_2SO_4), filtered and concentrated. The concentrate was purified by flash column chromatography on silica gel using DCM as the eluant to afford 2.02 g (74%) of the desired product as an orange solid.

Example 1D2-(4-fluorophenyl)-3-(4-pyridinyl)cyclohepta[b]pyrrole

A mixture of Example 1B (0.93 mmol), Example 1C (0.90 mmol), ammonium acetate (2.8 mmol), TEA (1.3 mmol) and 4 Å molecular sieves in benzene (1 mL) was heated to 65-80 °C for 6 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and extracted with 1N H_3PO_4 (25 mL). The aqueous layer was washed with ethyl acetate (25 mL), made basic with saturated K_2CO_3 , and extracted with ethyl acetate (2 x 25 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated. The concentrate was purified by column chromatography on silica gel using

50% hexanes/ethyl acetate as the eluant to afford 360 mg of the desired product as a red solid.

¹H NMR (400 MHz, CDCl₃): δ 7.13 (m, 2H), 7.39 (dd, 2H, J=4.7, 1.7 Hz), 7.67 (m, 1H), 7.67 (dd, 1H, J=8.4, 5.1 Hz), 7.80 (t, 1H, 9.6 Hz), 7.95 (t, 1H, J=9.6 Hz), 8.04 (t, 1H, J=9.6 Hz), 8.45 (d, 1H, J=10.4 Hz), 8.61 (dd, 2H, J=4.4, 1.6 Hz), 8.71 (d, 1H, J=8.8 Hz).
¹³C NMR (100 MHz, CDCl₃): δ 166.2, 163.9, 158.6, 150.7, 146.2, 145.2, 140.6, 137.5, 136.0, 133.2, 132.5, 132.2, 132.1, 127.4, 123.0, 116.6.
MS (ESI): *m/e* 301(M+1)⁺.

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Example 22-(4-fluorophenyl)-3-(2-fluoropyridin-4-yl)cyclohepta[b]pyrroleExample 2A1-(4-fluorophenyl)-2-(2-fluoro-4-pyridinyl)ethanone

15 The title compound was prepared according to the method described in Example 1B, substituting 2-fluoro-4-methylpyridine for 4-methylpyridine to afford the desired product.

¹H NMR (300 MHz, CDCl₃): δ 4.3 (s, 2H), 6.85 (s, 1H), 7.10 (d, J=4.8 Hz, 1H), 7.1-7.2 (m, 2H), 8.0-8.1 (m, 2H), 8.20 (d, J=5.1 Hz, 1H).
20 MS (ESI): *m/e* 234 (M+1)⁺.

Example 2B2-(4-fluorophenyl)-3-(2-fluoropyridin-4-yl)cyclohepta[b]pyrrole

25 The title compound was prepared according to the method described in Example 1D, substituting Example 2A for Example 1B to afford the desired product.

¹H NMR (300 MHz, CDCl₃): δ 7.0 (s, 1H), 7.10 (t, J=8.4 Hz, 2H), 7.20 (d, J=5.1 Hz, 1H), 7.7-7.85 (m, 3H), 7.8-8.0 (m, 2H), 8.30 (d, J=5.1 Hz, 1H), 8.40 (d, J=10.2 Hz, 1H), 8.85 (bs, 1H).

MS (ESI): *m/e* 319 (M+1)⁺.

30

Example 33-pyridin-4-yl-2-(3-(trifluoromethyl)phenyl)cyclohepta[b]pyrroleExample 3A5 N-methoxy-N-methyl-3-(trifluoromethyl)benzamide

The title compound was prepared according to the method described in Example 1A, substituting meta-trifluoromethylbenzoyl chloride for para-fluorobenzoyl chloride to afford the desired product.

10 Example 3B2-(4-pyridinyl)-1-(3-(trifluoromethyl)phenyl)ethanone

The title compound was prepared according to the method described in Example 1B, substituting Example 3A for Example 1A to afford the desired product.

15 ¹H NMR (400MHz, CDCl₃): δ 4.30 (s, 2H), 7.20 (d, J=6.0 Hz, 2H), 7.65 (t, J=8 Hz, 1H), 7.85 (d, J=8.0 Hz, 1H), 8.15 (d, J=8.0 Hz, 1H), 8.25 (s, 1H), 8.60 (d, J=6.0 Hz, 2H).
MS (ESI): *m/e* 266 (M+1)⁺.

Example 3C3-pyridin-4-yl-2-(3-(trifluoromethyl)phenyl)cyclohepta[b]pyrrole

20 The title compound was prepared according to the method described in Example 1D, substituting Example 3B for Example 1B to afford the desired product.

¹H NMR (300 MHz, CDCl₃): δ 7.35 (d, 2H), 7.50 (t, J=7.8 Hz, 1H), 7.65 (d, J=7.8 Hz, 1H), 7.75 (t, J=9.9 Hz, 1H), 7.9-9.0 (m, 3H), 8.20 (s, 1H), 8.45 (d, J=10.2 Hz, 1H), 8.70 (s, 2H), 8.95 (bd, 1H).

25 MS (ESI): *m/e* 351 (M+1)⁺.

Example 42-(4-fluorophenyl)-3-(2-(methylsulfanyl)-4-pyrimidinyl)cyclohepta[b]pyrrole

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Example 4A4-methyl-2-(methylsulfanyl)pyrimidine

Example 4A was prepared according to the method described in WO 97/35856.

Briefly, a mixture of 4-methylpyrimidine-2-thiol hydrochloride (5 g, 30.7 mmol), N,N-dimethylacetamide dimethyl acetal (5 mL, 37.6 mmol) and diisopropylethylamine (8 mL, 45.9 mmol) in toluene (10 mL) was refluxed for 3 hours. The reaction mixture was cooled to room temperature and then concentrated. The concentrate was diluted with diethyl ether and washed with saturated aqueous NaHCO₃ (50 mL). The aqueous layer was back extracted with diethyl ether (3x50 mL). The combined diethyl ether layers were dried (MgSO₄), filtered and concentrated. The concentrate was purified by silica gel chromatography using 50% hexanes/ethyl acetate to afford 3.6 g (83%) of the desired product as a clear yellow liquid.

¹H NMR (300 MHz, CDCl₃): δ 2.44 (s, 3H), 2.53 (s, 3H), 7.0 (d, J=5.4 Hz, 1H), 8.40 (d, J=5.7 Hz, 1H).

MS (ESI): *m/e* 284 (M+1)⁺.

20

Example 4B1-(4-fluorophenyl)-2-(2-(methylsulfanyl)-4-pyrimidinyl)ethanone

The title compound was prepared according to the method described in Example 1B, substituting 4-methyl-2-(methylsulfanyl)pyrimidine for 4-methylpyridine to afford the desired product.

¹H NMR (300 MHz, CD₃OD): δ 2.60 (s, 3H), 6.95 (d, J=5.4 Hz, 1H), 7.15-7.25 (m, 2H), 7.9-8.0 (m, 2H), 8.40 (d, J=5.7 Hz, 1H).

MS (ESI): *m/e* 263 (M+1)⁺.

Example 4C2-(4-fluorophenyl)-3-(2-(methylsulfanyl)-4-pyrimidinyl)cyclohepta[b]pyrrole

The title compound was prepared according to the method described in Example 1D, substituting Example 4B for Example 1B to afford the desired product.

5 ¹H NMR (300 MHz, CDCl₃): δ 2.60 (s, 3H), 6.90 (d, J=5.1 Hz, 1H), 7.15 (t, J=8.4 Hz, 2H), 7.8-8.1 (m, 5H), 8.45 (d, J=5.1 Hz, 1H), 9.0 (bd, 1H), 9.25 (d, J=10.2 Hz, 1H);
MS (ESI): *m/e* 348 (M+1)⁺.

Example 54-(2-(4-fluorophenyl)cyclohepta[b]pyrrol-3-yl)-N-methyl-2-pyrimidinamine

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Example 5A4-(2-(4-fluorophenyl)cyclohepta[b]pyrrol-3-yl)-N-methyl-2-pyrimidinamine

Oxone (200 mg, 0.32 mmol) in water (1.5 mL) was added dropwise over a 5 minute period to a -8 °C solution of Example 4C (100 mg, 0.25 mmol) in THF (1 mL).

15 After stirring for 2 minutes, the reaction mixture was quenched with a mixture of 10% aqueous NaOH (10 mL), ice and ethyl acetate (10 mL). The organic layer was separated, dried (MgSO₄), filtered and concentrated. The concentrate was dissolved in THF (1 mL) and treated with a room temperature solution of 40% aqueous methylamine (1 mL). The reaction mixture was stirred for 16 hours then concentrated. The concentrate was purified
20 by column chromatography on silica gel 20% MeCN:DCM to afford 19 mg of the desired compound as a red solid.

'H NMR (300 MHz, CDCl₃): δ 3.09 (d, J=5.1 Hz, 3H), 5.26 (m, 1H), 6.51 (d, J=5.1 Hz, 1H), 7.13 (m, 2H), 7.77 (apparent t, J=9.0 Hz, 1H), 7.84-7.99 (m, 4H), 8.26 (d, J=5.1 Hz, 1H), 8.85 (d, J=9.0 Hz, 1H), 9.11 (m, 1H).

25 MS (ESI): *m/e* 331(M+1)⁺.

Example 6N-methyl-4-{2-(3-(trifluoromethyl)phenyl)cyclohepta[b]pyrrol-3-yl}pyrimidin-2-amine

5

Example 6A3-(trifluoromethyl)phenyl-2-(2-(methylsulfanyl)-4-pyrimidinyl)ethanone

The title compound was prepared according to the method described in Example 1B, substituting 4-methyl-2-(methylsulfanyl)pyrimidine for 4-methylpyridine and Example 3A for Example 1A to afford the desired product.

10 ^1H NMR (300 MHz, CD_3OD): δ 2.60 (s, 3H), 6.95 (d, $J=5.4$ Hz, 1H), 7.6-7.7 (t, $J=7.8$ Hz, 1H), 7.90 (d, $J=7.8$ Hz, 1H), 8.15 (d, $J=7.8$ Hz, 1H), 8.16 (s, 1H), 8.39 (d, $J=5.7$ Hz, 1H).
MS (ESI): m/e 313 ($\text{M}+1$)⁺.

Example 6B2-(3-trifluorophenyl)-3-(2-(methylsulfanyl)-4-pyrimidinyl)cyclohepta[b]pyrrole

The title compound was prepared according to the method described in Example 1D, substituting Example 6A for Example 1B to afford the desired product.

15 ^1H NMR (300 MHz, CDCl_3): δ 2.60 (s, 3H), 6.90 (d, $J=5.1$ Hz, 1H), 7.55 (t, $J=7.8$ Hz, 1H), 7.70 (d, $J=7.8$ Hz, 1H), 7.85-8.1 (m, 4H), 8.15 (s, 1H), 8.45 (d, $J=5.4$ Hz, 1H), 8.95 (bd, $J=9.6$ Hz, 1H), 9.30 (d, $J=9.9$ Hz, 1H).
MS (ESI): m/e 398($\text{M}+1$)⁺.

Example 6CN-methyl-4-{2-(3-(trifluoromethyl)phenyl)cyclohepta[b]pyrrol-3-yl}pyrimidin-2-amine

25 The title compound was prepared according to the method described in Example 5A, substituting Example 6B for Example 4C to afford the desired product.

1 ^1H NMR (300 MHz, CDCl_3): δ 3.10 (d, $J=4.8$ Hz, 3H), 5.40 (bs, 1H); 6.50 (d, $J=5.1$ Hz, 1H), 7.55 (t, $J=7.5$ Hz, 1H), 7.70 (d, $J=7.8$ Hz, 1H), 7.8-8.05 (m, 4H), 8.20 (s, 1H), 8.25 (d, $J=4.5$ Hz, 1H), 9.0 (bd, 1H), 9.20 (bd, 1H).
30 MS (ESI): m/e 381($\text{M}+1$)⁺.

Example 73-(2-fluoropyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)cyclohepta[b]pyrroleExample 7A2-(2-fluoro-4-pyridinyl)-1-(3-(trifluoromethyl)phenyl)ethanone

The title compound was prepared according to the method described in Example 1B, substituting 2-fluoro-4-methylpyridine for 4-methylpyridine and substituting Example 3A for Example 1A to afford the desired product.

¹H NMR (300 MHz, CD₃OD): δ 4.35 (s, 2H), 6.85 (s, 1H), 7.10 (d, J=5.1 Hz, 1H), 7.6-7.7 (t, J=7.8 Hz, 1H), 7.90 (d, J=7.8 Hz, 1H), 8.15-8.25 (m, 3H).
MS (ESI): *m/e* 284 (M+1)⁺.

Example 7B3-(2-fluoropyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)cyclohepta[b]pyrrole

The title compound was prepared according to the method described in Example 1D, substituting Example 7A for Example 1B to afford the desired product.

¹H NMR (300 MHz, CDCl₃): δ 7.01 (s, 1H), 7.19 (d, 1H, J=4.8 Hz), 7.49 (t, 1H, J=7.8 Hz), 7.67 (d, 1H, J=7.8 Hz), 7.75 (t, 1H, J=9.3 Hz), 7.84 (d, 1H, J=7.8 Hz), 7.91 (t, 1H, J=9.3 Hz), 7.98 (dd, 1H, J=9.9, 9.0 Hz), 8.19 (s, 1H), 8.33 (d, 1H, J=5.1 Hz), 8.44 (d, 1H, J=9.9 Hz), 8.86 (d, 1H, J=9.3 Hz).
MS (ESI): *m/e* 369 (M+1)⁺.

Example 82-(4-methoxyphenyl)-3-pyridin-4-ylcyclohepta[b]pyrrole

25

Example 8A2-chloro-2,4,6-cycloheptatrien-1-one

Example 8A was prepared according to the method described in *J. Chem. Soc. C*. 1968, 1969. Briefly, thionyl chloride (3.0 mL, 41.4 mmol) and 2,4,6-Cycloheptatrien-1-one (5 g, 40.9 mmol) in benzene (100 mL) were refluxed for 1.5 hours and then

concentrated. The brown concentrate was triturated with hot hexanes (5x200 mL). The hexanes layers were combined and upon cooling, afforded 3 g (52%) of the desired product as yellow needles.

5

Example 8B2-(4-methoxyphenyl)-3-pyridin-4-ylcyclohepta[b]pyrrole

n-Butyllithium in hexanes (2.5M, 440 μ L, 1.1mmol) was added to a -78 °C solution of diisopropylamine (168 μ L, 1.2 mmol) in THF (2 mL). After stirring for 20 minutes,

10 4-methylpyridine (97 μ L, 1 mmol) was added to the reaction mixture. After stirring for 15 minutes, a solution of para-methoxybenzonitrile (111 mg, 1 mmol) in THF (0.5 mL) was added dropwise to the reaction mixture. After stirring for 30 minutes at -50 °C, Example 8A (168 mg, 1.2 mmol) in THF (0.5 mL) was slowly added to the reaction mixture. The reaction mixture was warmed to room temperature and stirred for 6 hours. The reaction
15 mixture was extracted with 1N H₃PO₄ (25 mL). The aqueous layer was washed with ethyl acetate (25 mL), basified with saturated aqueous K₂CO₃ and extracted with ethyl acetate (2x25 mL). The combined extracts were dried (MgSO₄), filtered, and concentrated. The concentrate was purified by column chromatography on silica gel using a gradient of 14 % acetone in hexanes to 75 % acetone in hexanes as the eluant to afford 28 mg of the desired
20 product as a red solid.

¹H NMR (300 MHz, CDCl₃): δ 3.88 (s, 3H), 6.9-7.15 (m, 4H), 7.35-7.44 (m, 1H), 7.5-7.58 (m, 2H), 7.6-7.7 (m, 1H), 7.95-8.05 (m, 1H), 8.2-8.32 (m, 1H), 8.48-8.65 (m, 2H), 8.8-8.85 (m, 1H).

MS (DCI/NH₃): *m/e* 313 (M+1)⁺.

25 Analysis calculated for C₂₁H₁₆N₂O·1.25 H₂O: C, 75.31; H, 5.56; N, 8.36. Found: C, 75.28; H, 5.61; N, 8.23.

Example 92-(4-chlorophenyl)-3-pyridin-4-ylcyclohepta[b]pyrrole

5

Example 9A2-(4-chlorophenyl)-3-pyridin-4-ylcyclohepta[b]pyrrole

The title compound was prepared according to the method described in Example 8B, substituting para-chlorobenzonitrile for para-methoxybenzonitrile to afford the desired product.

10 ^1H NMR (300 MHz, CDCl_3): δ 7.00-7.15 (m, 1H), 7.35-7.52 (m, 5H), 7.58-7.68 (m, 1H), 7.84-7.96 (m, 2H), 8.1-8.2 (m, 1H), 8.28-8.45 (m, 1H), 8.55-8.70 (m, 1H), 8.82-8.92 (m, 1H).

MS (DCI/ NH_3): m/e 317 ($\text{M}+1$) $^+$.

Analysis calculated for $\text{C}_{20}\text{H}_{13}\text{N}_2 \cdot 1.25 \text{ H}_2\text{O}$: C, 69.86; H, 4.69; N, 8.14. Found: C, 70.10; 15 H, 4.39; N, 8.35.

Example 102-(3-chlorophenyl)-3-pyridin-4-ylcyclohepta[b]pyrrole

20

Example 10A2-(3-chlorophenyl)-3-pyridin-4-ylcyclohepta[b]pyrrole

The title compound was prepared according to the method described in Example 8B, substituting meta-chlorobenzonitrile for para-methoxybenzonitrile to afford the desired product.

25 ^1H NMR (300 MHz, CDCl_3): δ 6.85-6.95 (m, 1H), 7.25-7.5 (m, 5H), 7.82-7.92 (m, 1H), 8.0-8.2 (m, 2H), 8.4-8.5 (m, 1H), 8.55-8.64 (m, 1H), 8.72-8.82 (m, 1H), 9.4-9.5 (m, 1H); MS (DCI/ NH_3): m/e 317 ($\text{M}+1$) $^+$.

Analysis calculated for $\text{C}_{20}\text{H}_{13}\text{N}_2 \cdot 1.5 \text{ H}_2\text{O}$: C, 69.86; H, 4.69; N, 8.14. Found: C, 69.81; H, 4.47; N, 8.18.

Example 112-(3-chlorophenyl)-3-(2-fluoropyridin-4-yl)cyclohepta[b]pyrroleExample 11A2-(3-chlorophenyl)-3-(2-fluoropyridin-4-yl)cyclohepta[b]pyrrole

5 The title compound was prepared according to the method described in Example 8B, substituting 2-fluoro-4-methylpyridine for 4-methylpyridine to afford the desired product.

10 ^1H NMR (300 MHz, CDCl_3): δ 7.1-7.5 (m, 7H), 8.0-8.1 (m, 2H), 8.30 (d, 1H), 8.60 (d, 1H), 8.80 (d, 1H); MS (ESI): *m/e* 335(M+1)⁺.

Example 122-(4-methylphenyl)-3-pyridin-4-ylcyclohepta[b]pyrroleExample 12A2-(4-methylphenyl)-3-pyridin-4-ylcyclohepta[b]pyrrole

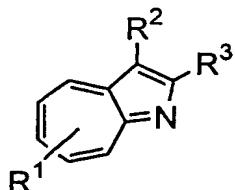
15 The title compound was prepared according to the method described in Example 8B, substituting para-methylbenzonitrile for para-methoxybenzonitrile to afford the desired product.

20 ^1H NMR (300 MHz, CDCl_3): δ 2.38 (s, 3H), 7.18 (d, $J=7.5$ Hz, 2H), 7.35 (d, $J=6$ Hz, 2H), 7.60-7.75 (m, 3H), 7.80-7.85 (m, 2H), 8.35 (d, $J=10.5$ Hz, 1H), 8.73 (d, $J=6$ Hz, 2H), 8.85 (br d, $J=9$ Hz, 1H).
MS (DCI/NH₃): *m/e* 297 (M+1)⁺.

25 It will be evident to one skilled in the art that the instant invention is not limited to the forgoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, and all changes which come within the meaning and range of equivalency of the claims and therefore intended to be embraced therein.

WHAT IS CLAIMED IS:

1. A compound of formula (I)



(I),

5 or a pharmaceutically acceptable salt or prodrug thereof, wherein

R^1 is selected from the group consisting of hydrogen, amino, hydroxy, hydroxyalkyl, and $CH_3S(O)_t$ -, wherein t is zero, one, or two;

10 R^2 and R^3 are independently selected from the group consisting of phenyl, naphthyl, furyl, thiophenyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidyl, and pyrazinyl, wherein the groups defining R^2 can be optionally substituted with one, two, or three substituents independently selected from the group consisting of C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_6 perfluoroalkyl, hydroxy, C_1 - C_3 alkoxy, trifluoromethoxy, trifluorothiomethoxy, cyano, nitro, carboxyl, and amino, and wherein the groups defining R^3 can be optionally substituted with one, two, or three substituents independently selected from the group consisting of carboxyl, cyano, halide, nitro, hydroxyl, oxo, C_1 - C_6 perfluoroalkoxy, sulfonic, C_1 - C_6 perfluoroalkyl, C_1 - C_6 perfluorothioalkoxy, sulphydryl, thiolcarboxyl, thioxo, $-L^1-L^2-R^4$, and $-L^1-L^3-R^5$;

15 L^1 is absent or $-L^4-(C_1-C_6\text{ alkylene})-$;

20 L^2 is selected from the group consisting of $-C(=O)(NR^6)-$, $-C(=O)-S-$, $-N(R^6)-$, $=N-$, $-O-C(=O)-N(R^6)-$, $=N-N(R^6)-$, $-N(R^6)-N(R^6)-$, $N(R^6)-C(=NR^6)-N(R^6)-$, $=N-O-$, $=N-N(R^6)-C(=O)-N(R^6)-$, and $-N(R^6)-C(=O)-N(R^6)-$;

25 L^3 is absent or selected from the group consisting of $-L^2-$, $-C(=O)-$, $-O-C(=O)-$, $-N(R^6)-C(=O)-$, $-N(R^6)-C(=O)-O-$, $-O-$, $-S-C(=O)-$, $-O-C(=O)-O-$, $=N(R^6)-O-$, $-O-C(=N(R^6))-$, $-N(R^6)-C(=NR^6)-$, $-C(=O)-O-C(=O)-$ and $-S(O)_t-$, wherein n is zero, one, or two;

30 L^4 is absent or is selected from the group consisting of $-O-$, $-S(O)_t$ -, and $-N(R^6)-$;

R^4 is hydrogen or C_1 - C_6 alkyl;

R^5 is selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, cycloalkylalkyl, and arylalkyl;

and

5 R^6 is selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, cycloalkylalkyl, and arylalkyl.

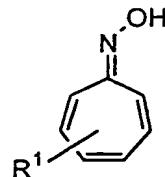
2. A compound according to Claim 1, wherein R^1 is hydrogen.

10 3. A compound according to Claim 1, wherein R^2 is optionally substituted pyridyl.

4. A compound according to Claim 1, wherein R^2 is optionally substituted pyrimidinyl.

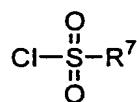
15 5. A compound according to Claim 1, wherein R^3 is optionally substituted phenyl.

6. A method for preparing a compound of formula (I) comprising
(a) reacting a compound of formula (II)



20 (II)

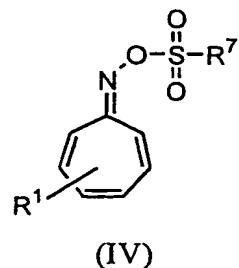
with a compound of formula (III)



(III),

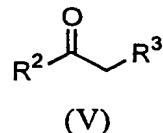
25 wherein R^7 is selected from the group comprising methyl, trifluoromethyl, and phenyl, wherein the phenyl group can be optionally substituted with a substituent selected

from the group comprising methyl, bromo, and nitro, and a first base to provide a compound of formula (IV)



5 and

(b) reacting the product of step (a) with a compound of formula (V)



and a second base.

10

7. The method of Claim 6, wherein R⁷ is 4-methylphenyl.

15

8. The method of Claim 6, wherein the first base is selected from the group comprising triethylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, lutidine, pyridine, N,N-dimethylaminopyridine, and mixtures thereof.

9. The method of Claim 8, wherein the first base is triethylamine.

20

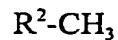
10. The method of Claim 6, wherein the second base is selected from the group comprising triethylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, lutidine, pyridine, ammonium acetate, N,N-dimethylaminopyridine, and mixtures thereof.

11. The method of Claim 10, wherein the second base is a mixture of triethylamine and ammonium acetate.

25

12. A method for preparing a compound of formula (I) comprising

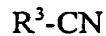
(a) reacting a compound of formula (VI)



(VI)

with a third base;

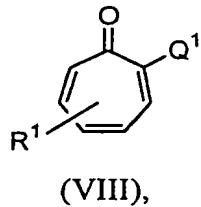
5 (b) reacting the product of step (a) with a compound of formula (VII)



(VII);

and

(c) reacting the product of step (b) with a compound of formula (VIII)



(VIII),

wherein Q¹ is selected from the group comprising chlorine, bromine and iodine.

13. The method of Claim 12, wherein the third base is selected from the group

15 comprising lithium diisopropylamine, lithium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, and tertiary-butyllithium.

14. The method of Claim 13, wherein the base is lithium diisopropylamine.

20 15. A method of inhibiting p38 MAP kinase in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of Claim 1.

25 16. A method of treating inflammatory diseases in a mammal, in recognized need of such treatment, comprising administering to the mammal a therapeutically effective amount of a compound of Claim 1.

17. A method of inhibiting TNF-alpha production in a mammal, in recognized need of such treatment, comprising administering to the mammal a therapeutically effective amount of a compound of Claim 1.

5 18. A method of treating inflammatory diseases in a mammal, in recognized need of such treatment, comprising administering to the mammal a therapeutically effective amount of a compound of Claim 1 in the presence of a pharmaceutically acceptable carrier.

10 19. A compound selected from the group consisting of
2-(4-fluorophenyl)-3-(4-pyridinyl)cyclohepta[b]pyrrole,
2-(4-fluorophenyl)-3-(2-fluoropyridin-4-yl)cyclohepta[b]pyrrole,
3-pyridin-4-yl-2-(3-(trifluoromethyl)phenyl)cyclohepta[b]pyrrole,
2-(4-fluorophenyl)-3-(2-(methylsulfanyl)-4-pyrimidinyl)cyclohepta[b]pyrrole,
15 4-(2-(4-fluorophenyl)cyclohepta[b]pyrrol-3-yl)-N-methyl-2-pyrimidinamine,
N-methyl-4-{2-(3-(trifluoromethyl)phenyl)cyclohepta[b]pyrrol-3-yl}pyrimidin-2-amine,
3-(2-fluoropyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)cyclohepta[b]pyrrole,
2-(4-methoxyphenyl)-3-pyridin-4-ylcyclohepta[b]pyrrole,
20 2-(4-chlorophenyl)-3-pyridin-4-ylcyclohepta[b]pyrrole,
2-(3-chlorophenyl)-3-pyridin-4-ylcyclohepta[b]pyrrole,
2-(3-chlorophenyl)-3-(2-fluoropyridin-4-yl)cyclohepta[b]pyrrole, and
2-(4-methylphenyl)-3-pyridin-4-ylcyclohepta[b]pyrrole.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/02944

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/04 A61K31/403 C07D403/04 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 81, no. 5, 1974 Columbus, Ohio, US; abstract no. 25484w, page 25490; XP002168063 & YOSHIDA, N. ; TOMITA, K.: YAKUGAKU ZASSHI, vol. 94, no. 2, 1974, pages 199-203, abstract ---	1-19
A	WO 98 47899 A (ORTHO MCNEIL CORP INC) 29 October 1998 (1998-10-29) the whole document ---	1-19
A	EP 0 376 223 A (KAKEN PHARMA CO LTD) 4 July 1990 (1990-07-04) the whole document ---	1-19

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

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- *&* document member of the same patent family

Date of the actual completion of the international search

22 May 2001

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No

PCT/US 01/02944

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
WO 9847899	A 29-10-1998	AU	7132998	A	13-11-1998
EP 0376223	A 04-07-1990	JP	2178263	A	11-07-1990
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